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Comparative study of amino acid, ammonia and pancreatic hormone levels in the blood of cirrhotic patients following intragastric and intravenous administration of a branched-chain amino acid-enriched solution.

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# Comparative study of amino acid, ammonia and pancreatic hormone levels in the blood of cirrhotic patients following intragastric and intravenous administration of a branched-chain amino acid-enriched solution.\*

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## Abstract

The blood levels of amino acids, ammonia and pancreatic hormones following the intragastric and intravenous administration of a branched-chain amino acid (BCAA)-enriched solution were comparatively investigated in control subjects and patients with liver cirrhosis. There was no essential difference in the time course of serum amino acid and blood ammonia levels between the intragastric and intravenous infusions. Elevation of serum insulin concentrations in cirrhotic patients was significant only immediately after the administration through the enteral route. However, plasma glucagon levels increased similarly when the BCAA-enriched solution was administered through either route. The results indicate that both enteral and intravenous infusions will have similar therapeutic effects on the impaired protein metabolism in cirrhotic patients with protein-calorie malnutrition.

**KEYWORDS:** amino acid, pancreatic hormone, ammonia, liver cirrhosis, intragastric and intravenous infusion

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— BRIEF NOTE —

**COMPARATIVE STUDY OF AMINO ACID, AMMONIA AND  
PANCREATIC HORMONE LEVELS IN THE BLOOD OF  
CIRRHOTIC PATIENTS FOLLOWING INTRAGASTRIC  
AND INTRAVENOUS ADMINISTRATION OF  
A BRANCHED-CHAIN AMINO  
ACID-ENRICHED SOLUTION**

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*Abstract.* The blood levels of amino acids, ammonia and pancreatic hormones following the intragastric and intravenous administration of a branched-chain amino acid (BCAA)-enriched solution were comparatively investigated in control subjects and patients with liver cirrhosis. There was no essential difference in the time course of serum amino acid and blood ammonia levels between the intragastric and intravenous infusions. Elevation of serum insulin concentrations in cirrhotic patients was significant only immediately after the administration through the enteral route. However, plasma glucagon levels increased similarly when the BCAA-enriched solution was administered through either route. The results indicate that both enteral and intravenous infusions will have similar therapeutic effects on the impaired protein metabolism in cirrhotic patients with protein-calorie malnutrition.

*Key words :* amino acid, pancreatic hormone, ammonia, liver cirrhosis, intragastric and intravenous infusion.

The characteristic amino acid patterns in the blood and cerebrospinal fluid (CSF) of patients with liver cirrhosis have been described (1, 2) and may be a factor in pathogenesis of hepatic encephalopathy. Elevated levels of serum aromatic amino acids (AAA) and methionine and depressed concentrations of branched-chain amino acids (BCAA) were observed in advanced liver cirrhosis. Use of special amino acid mixture containing a high proportion of BCAA and low proportion of AAA and methionine has aided in the control of hepatic encephalopathy by correcting the abnormal serum and CSF aminograms (1, 2). Hyperammonemia in patients with liver cirrhosis may contribute to the neutral amino acid imbalance, probably because ammonia induces hyperglucagonemia and then hyperinsulinemia leading to the stimulated catabolism of BCAA in the muscle (3). Therefore, serum amino acid imbalance, hyperammonemia and elevated pancreatic hormone levels might be closely related to each other and affect the pathophysiology of the cirrhotic liver.

We have used this type of synthetic amino acid solution as an intravenous alimentation and elemental diet for the nutritional support of cirrhotic patients with protein-calorie malnutrition (4). In the present study, amino acid, ammonia and pancreatic hormone concentrations in the blood were determined and compared following the intragastric and intravenous administration of a BCAA-enriched solution to control subjects and cirrhotic patients.

The diagnosis for the 5 patients with compensated liver cirrhosis (serum cholinesterase  $0.31 \pm 0.1$   $\Delta$ pH and  $K_{\text{ICG}} 0.07 \pm 0.02$ ) adopted for this study were based on liver biopsy. A BCAA-enriched amino acid solution (Fischer solution, 84 g amino acid per l : leucine, 11.0 ; valine, 8.4 ; isoleucine, 9.0 ; methionine, 1.0 ; phenylalanine, 1.0 ; tryptophan, 0.8 ; arginine, 7.3 ; lysine, 7.6 ; threonine, 1.5 ; alanine, 7.5 ; histidine, 3.2 ; proline, 8.0 ; serine, 5.0 ; glycine, 9.0, and cystine, 0.4 g) was intravenously and intragastrically infused at a dose of 500 ml in the early morning for 3 h to the 3 control subjects and 5 cirrhotic patients. No glucose was infused. Serum amino acid and insulin, blood ammonia and plasma glucagon levels were determined immediately and 3 h after the end of the 3-h infusion.

Alterations in serum neutral amino acid levels following drip infusion of the BCAA-enriched solution to cirrhotic patients are summarized in Fig. 1. Serum BCAA levels immediately after the infusion were elevated 4 to 8-fold in both control and cirrhotic subjects and then returned to the level before the infusion. Tyrosine and phenylalanine levels were slightly lower 3 h after the infusion, but serum methionine concentrations had increased 2-fold immediately after the infusion to cirrhotic patients. However, there was no significant difference in the time course of the amino acid levels in cirrhotic patients whether the BCAA-enriched solution was administered intragastrically or intravenously. These patterns of serum neutral amino acid levels were similar to those observed in control subjects, except that the extent of BCAA increment was 3 to 6-fold over the basal levels and no elevation of serum methionine observed immediately after the intragastric infusion to controls. No essential difference between the two infusion routes was also observed in control subjects. These data suggest that neutral amino acid absorption from the gut is rapid and quantitative at least under the conditions of this study.

Blood ammonia concentrations were significantly elevated immediately after the stop of the intragastric administration of a BCAA-enriched solution to control and cirrhotic subjects, and the extent of the elevation was not different between the two methods of administration (Table 1). The blood ammonia levels 3 h after the cessation of the intragastric administration were significantly higher than those after the intravenous infusion. The blood ammonia levels are generally considered to rise following the intragastric feeding of amino acids because of portal-systemic shunting of ammonia produced in the intestine (6). The present observations indicate that there was little contribution of bacterial ammonia production in the

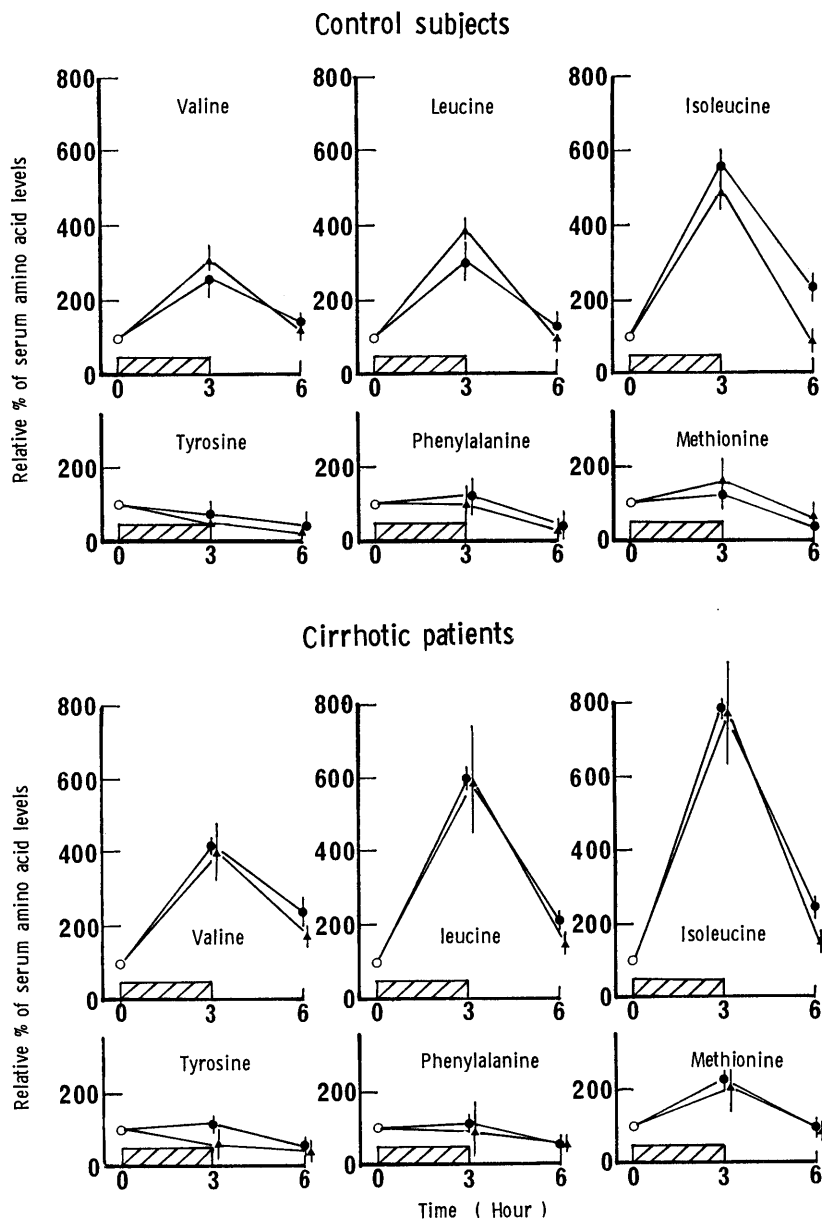


Fig. 1. Alterations in the serum neutral amino acid levels following the intragastric and intravenous administration of a BCAA-enriched solution to 3 control subjects and 5 cirrhotic patients. Experimental details are described above. ●—●, Intragastric and ▲—▲, intravenous administration. The vertical lines on each bar indicate the standard error of the mean. ▨ indicates the duration of the amino acid infusion.

TABLE 1. BLOOD AMMONIA LEVELS BEFORE AND AFTER THE INTRAVENOUS AND INTRAGASTRIC ADMINISTRATION OF A BCAA-ENRICHED SOLUTION TO 3 CONTROL SUBJECTS AND 5 CIRRHOTIC PATIENTS

Method of administration	Before the infusion	After the cessation of the infusion		
		Immediately	3 Hours	
(μg/dl)				
Liver cirrhosis				
Intravenous	61 ± 24	96 ± 58	41 ± 10	
Intragastric	53 ± 21	97 ± 30*	58 ± 31**	
Control subjects				
Intravenous	23 ± 10	42 ± 9	16 ± 10	
Intragastric	18 ± 6	38 ± 12	21 ± 3	

Asterisks denote  $p < 0.05$  and double asterisks  $p < 0.02$  over the values before the infusion and the values 3 hours after the stop of the intravenous injection, respectively.

TABLE 2. SERUM IRI AND PLASMA IRG LEVELS BEFORE AND AFTER THE INTRAVENOUS AND INTRAGASTRIC ADMINISTRATION OF A BCAA-ENRICHED SOLUTION TO 5 CIRRHOTIC PATIENTS

Method of administration	Before the infusion	After the cessation of the infusion	
		Immediately	3 Hours
IRI (nU/ml)			
Intravenous	13.0 ± 7.8	19.3 ± 12.5	9.2 ± 6.2
Intragastric	16.9 ± 7.2*	52.3 ± 29.0*	13.1 ± 8.9
IRG (pg/ml)			
Intravenous	182 ± 67	483 ± 368	318 ± 276
Intragastric	175 ± 77	459 ± 276	387 ± 412

IRI, immunoreactive insulin and IRG, immunoreactive glucagon. The antigen used for the IRG assay was 30 K for specific determination of pancreatic glucagon levels. The asterisks denote  $p < 0.02$  over the values before the infusion.

small and large intestine to the blood ammonia level when the amino acids were slowly infused into the stomach, since the ammonia levels rose similarly after the intravenous infusion.

Blood sugar levels were not significantly changed in control subjects and cirrhotic patients before and after the feeding of amino acids. Serum insulin levels were elevated immediately after the 3-h drip infusion to cirrhotic patients and then slightly diminished below the levels before the infusion (Table 2). The extent of insulin elevation was much greater when amino acids were infused through the enteral route than the intravenous route. It is well known that oral administration of glucose induces much higher insulin levels than intravenous administration (6). The direct contact of a BCAA-enriched solution with the gastroduodenal mucous membrane stimulates insulin secretion, although the exact

mechanism is not known. That there was no difference in the amounts of amino acids absorbed between the different infusion routes can explain the marked elevation of serum insulin levels observed only in the case of the intragastric route. Plasma glucagon levels were insignificantly high immediately after, and the mean values remained high at least for 3 h after the end of the infusion. No significant difference in the time course of plasma glucagon levels was observed between the two routes of amino acid administration. The intragastric feeding of amino acids may not result in the accelerated excretion of enteroglucagon.

Comparative studies on nutrition management by enteral diet or intravenous alimentation have been conducted (7). Several reports suggest that the different methods of administration similarly maintain and improve the general nutritional condition (8). No essential difference in amino acid, ammonia and glucagon levels following the administration by different routes of amino acids indicates that the enteral and intravenous infusion will have similar therapeutic effects on cirrhotic liver. This is consistent with Hayashi's conclusion based on experimental studies of nutrition management in acute and chronic liver injury (9).

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